THE
MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

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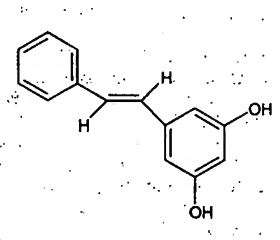
A. A. Loman, L. R. Snowdon, *Can. J. Chem.* **48,** 1554 (1970). Biosynthesis: Birch, *Fortschr. Chem. Org. Naturst.* **14,** 186 (1957). Toxicological study: K. O. Frykholm, *Nature* **155,** 454 (1945). Use as antimicrobial agent: E. H. Sheers, **DE 1952451**; *idem,* **US 3577230** (1970, 1971 both to Arizona Chem. Co.). Deterrent to feeding behavior of snowshoe hare: J. P. Bryant *et al., Science* **222,** 1023 (1983).

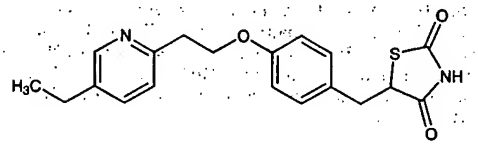


Fine needles from glacial acetic acid, mp 155.5-156°. uv max (ethanol): 305 nm (log ε 4.49). Practically insol in water. Sol in benzene, acetone, chloroform, glacial acetic acid.

Monomethyl ether. $C_{15}H_{14}O_2$. Crystals, mp 122-123°. uv max (ethanol): 303 nm (log ε 4.26). More sol in benzene than pinosylvin. Also sol in methanol, glacial acetic acid.

Dimethyl ether. $C_{16}H_{16}O_2$. Crystals from methanol-water, mp 55-56°. uv max (ethanol): 305 nm (log ε 4.39).

7533. Pioglitazone. [111025-46-8] 5-[[4-[2-(5-Ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione; (±)-5-[*p*-[2-(ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione; AD-4833. $C_{19}H_{20}N_2O_3S$; mol wt 356.45. C 64.02%, H 5.66%, N 7.86%, O 13.47%, S 9.00%. Insulin sensitizer. Prepn: K. Meguro, T. Fujita, **EP 193256**; *eidem,* **US 4687777** (1986, 1987 both to Takeda); T. Sohda *et al., Arzneimittel-Forsch.* **40,** 37 (1990). Pharmacology: H. Ikeda *et al., ibid.* 156. HPLC determn in serum: W. Z. Zhong, D. B. Lakings, *J. Chromatog.* **490,** 377 (1989). Mechanism of action: C. Hofmann *et al., Endocrinology* **129,** 1915 (1991); M. Kobayashi *et al., Diabetes* **41,** 476 (1992). Effect on adipocyte differentiation: T. Sandouk *et al., Am J. Physiol.* **264,** C1600 (1993). Clinical evaluation in noninsulin-dependent diabetes: R. Kawamori *et al., Diabetes Res. Clin. Pract.* **41,** 35 (1998).

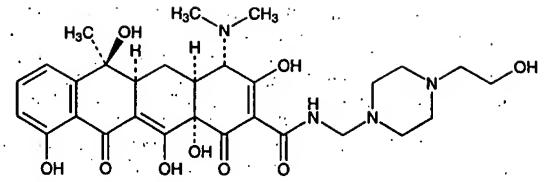


Colorless needles from DMF + water, mp 183-184°.

Hydrochloride. [112529-15-4] U-72107A; Actos. $C_{19}H_{20}N_2O_3S.HCl$; mol wt 392.91. Colorless prisms from ethanol, mp 193-194°. Sol in DMF; slightly sol in ethanol; very slightly sol in acetone, acetonitrile. Practically insol in water; insol in ether.

THERAP CAT: Antidiabetic.

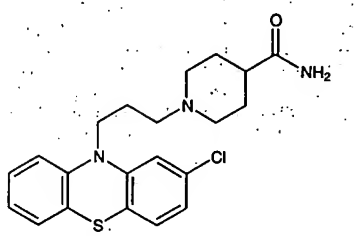
7534. Pipacycline. [1110-80-1] [4*S*-(4α,4aα,5aα,6β,12aα)]-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-*N*-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]-6-methyl-1,11-dioxo-2-naphthacenecarboxamide; *N*-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]tetracycline; *N*-[4-(β-hydroxyethyl)diethylenediamino-1-methyl]tetracycline; mepicycline; mepiciclina; Ambra-Vena; Sieromicin; Valtomicina. $C_{29}H_{38}N_4O_9$; mol wt 586.63. C 59.37%, H 6.53%, N 9.55%, O 24.55%. Semi-synthetic broad spectrum antibiotic related to tetracycline. Prepn: Pedrazzoli *et al., Boll. Chim. Farm.* **98,** 516 (1959), *C.A.* **54,** 3856a (1960); Gradnik *et al.,* **GB 888968** corresp to **US 3149114** (1962 and 1964 to E.R.A.S.M.E.). Properties: *eidem, Pharm. Acta Helv.* **35,** 529 (1960). Pharmacokinetic studies: A. Scalvini, A. Delmonte, *Gazz. Med. Ital.* **131,** 1 (1972).



Yellow cryst powder, dec 162-163°. $[\alpha]_D^{20}$ −195° (c = 0.5). $[\alpha]_D^{20}$ −175° (c = 0.5 in methanol). uv max (10 γ/ml 0.1*N* HCl): 286, 355 nm. pH of 2% aq soln, 7.2-7.4. Freely sol in water, methanol, formamide; slightly sol in ethanol, isopropanol. Practically insol in ether, benzene, chloroform. Sensitive to light, heat, and air. LD_{50} i.v. in white mice: 188 mg/kg (Scalvini, Delmonte).

THERAP CAT: Antibacterial.

7535. Pipamazine. [84-04-8] 1-[3-(2-Chloro-10*H*-phenothiazin-10-yl)propyl]-4-piperidinecarboxamide; 1-[3-(2-chlorophenothiazin-10-yl)propyl]isonipecotamide; 10-[3-(4-carbamoylpiperidin-1-yl)propyl]-2-chlorophenothiazine; 2-chloro-10-[3-(4-carbamoylpiperidinyl)propyl]phenothiazine; 10-[3-(4-carbamoylpiperidino)propyl]-2-chlorophenothiazine; SC-9387; Nausidol; Mornidine. $C_{21}H_{24}ClN_3OS$; mol wt 401.96. C 62.75%, H 6.02%, Cl 8.82%, N 10.45%, O 3.98%, S 7.98%. Prepn: Cusic *et al.,* **US 2957870** (1960 to Searle).

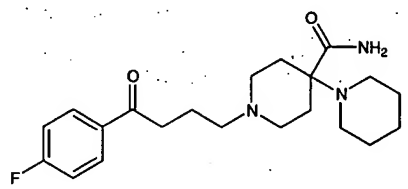


Crystals from 2-propanol + petr ether, mp about 139°.

Hydrochloride. Crystals, mp about 196-197° with formation of bubbles.

THERAP CAT: Antiemetic.

7536. Pipamperone. [1893-33-0] 1′-[4-(4-Fluorophenyl)-4-oxobutyl]-[1,4′-bipiperidine]-4′-carboxamide; 1′-[3-(*p*-fluorobenzoyl)propyl]-[1,4′-bipiperidine]-4′-carboxamide; 1-(*p*-fluorophenyl)-4-(4-piperidino-4-carbamoylpiperidino)-1-butanone; 1-[γ-(4-fluorobenzoyl)propyl]-4-piperidinopiperidine-4-carboxamide; 4′-fluoro-4-[*N*-[4-(*N*-piperidino)-4-carbamido]-piperidino]butyrophenone; floropipamide; R-3345. $C_{21}H_{30}FN_3O_2$; mol wt 375.48. C 67.17%, H 8.05%, F 5.06%, N 11.19%, O 8.52%. Prepn of the dihydrochloride by reaction of γ-chloro-4-fluorobutyrophenone and 4-piperidinopiperidine-4-carboxamide: Janssen, **BE 610830** (1962 to Janssen), *C.A.* **57,** 13740b (1962).



Dihydrochloride. [2448-68-2] Dipiperon; Piperonil; Propitan. $C_{21}H_{30}FN_3O_2.2HCl$; mol wt 448.41. Crystals, mp 124.5-126.0°.

THERAP CAT: Antipsychotic.

7537. Pipazethate. [2167-85-3] 10*H*-Pyrido[3,2-*b*]-[1,4]benzothiadiazine-10-carboxylic acid 2-(2-piperidinoeth-

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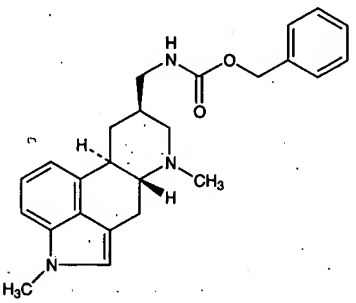
amino)methyl]-1,6-dimethylergoline I benzyl ester; D-*N*-carboxydihydro-1-methyllysergamine I benzyl ester; D-[(4,6,6a,-7,8,9,10,10a-octahydro-4,7-dimethyl-10aα-indolo[4,3-*fg*]quinolin-9β-yl)methyl]carbamic acid benzyl ester; methergoline; Liserdol; Contralac. $C_{25}H_{29}N_3O_2$; mol wt 403.52. C 74.41%, H 7.24%, N 10.41%, O 7.93%. Serotonin 5HT-receptor antagonist. Prepn: Bernardi *et al., Gazz. Chim. Ital.* **94,** 936 (1964); Camerino *et al.,* US **3238211** (1966 to Farmitalia). Pharmacology: C. Beretta *et al., Nature* **207,** 421 (1965). Metabolic studies: Arcamone *et al., Boll. Chim. Farm.* **110,** 704 (1971). Mode of action study: L. Krulich *et al., Endocrinology* **108,** 1115 (1981). Clinical antiprolactin activity: F. Scapin *et al., Eur. J. Clin. Pharmacol.* **22,** 181 (1982); A. Caballero *et al., J. Reprod. Med.* **32,** 115 (1987).

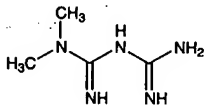


Crystals from benzene + ether, mp 146-149°. $[\alpha]_D^{28}$ −7 ±2°. uv max: 291 nm ($E_{1cm}^{1\%}$ 165). Very sol in pyridine; sol in alc, acetone, chloroform. Practically insol in benzene, ether, water. LD_{50} in mice (mg/kg): 85 i.p., 430 orally; in rats (mg/kg): >800 orally (Beretta).

THERAP CAT: Prolactin inhibitor.

THERAP CAT (VET): Prolactin inhibitor.

5963. Metformin. [657-24-9] *N,N*-Dimethylimidodicarbonimidic diamide; 1,1-dimethylbiguanide; *N,N*-dimethyldiguanide; *N'*-dimethylguanylguanidine; DMGG; LA-6023. $C_4H_{11}N_5$; mol wt 129.16. C 37.20%, H 8.58%, N 54.22%. Oral hypoglycemic agent. Prepn: Werner, Bell, *J. Chem. Soc.* **121,** 1790 (1922); Shapiro *et al., J. Am. Chem. Soc.* **81,** 3728 (1959). Use as antidiabetic: J. J. Sterne, US **3174901** (1965 to Jan Marcel Didier Aron-Samuel). Toxicity: *Rx Bulletin* **3,** 25 (1972). Pharmacokinetics in man: G. T. Tucker *et al., Brit. J. Clin. Pharmacol.* **12,** 235 (1981). Review of pharmacology: L. S. Hermann, *Diabete Metab.* **5,** 233-245 (1979). Efficacy in NIDDM: R. A. DeFronzo *et al., N. Engl. J. Med.* **333,** 541 (1995). Metabolic effects and mechanism of action study: M. Stumvoll *et al., ibid.* 550.



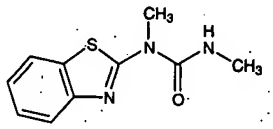
Hydrochloride. [1115-70-4] Diabetosan; Diabex; Glucophage; Metiguanide. $C_4H_{11}N_5.HCl$; mol wt 165.63. Prisms from water, mp 232° (Werner, Bell); crystals from propanol, mp 218-220° (uncorr) (Shapiro). Sol in water, 95% alcohol. Practically insol in ether, chloroform. LD_{50} in rats (mg/kg): 1000 orally, 300 s.c. (*Rx Bulletin*).

***p*-Chlorophenoxyacetate (salt).** [25672-33-7] Glucinan. $C_4H_{11}N_5.C_8H_7ClO_3$; mol wt 315.76.

Embonate. [34461-22-8] Metformin pamoate; Stagid. $(C_4H_{11}N_5)_2.C_{23}H_{16}O_6$; mol wt 646.70.

THERAP CAT: Antidiabetic.

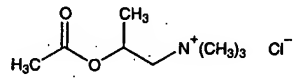
5964. Methabenzthiazuron. [18691-97-9] *N*-2-Benzothiazolyl-*N,N'*-dimethylurea; 1-(2-benzothiazolyl)-1,3-dimethylurea; metabenzthiazuron; MBU; Bayer 5633; Bayer 74283; Tribunil. $C_{10}H_{11}N_3OS$; mol wt 221.28. C 54.28%, H 5.01%, N 18.99%, O 7.23%, S 14.49%. Derivative of urea. Prepn and use as pre-emergence herbicide: N. E. Searle, US **2756135** (1956 to du Pont). Use as pre- and post-emergence herbicide in wheat and barley: H. Hack *et al.,* **GB 1085430** (1967 to Bayer). Herbicidal properties: H. Hack, *Pflanzenschutz-Nachr.* **22,** 331 (1969). Toxicity studies: G. Kimmerle, E. Löser, *ibid.* 351. Use in winter cereals: D. C. Clark *et al., Proc. 12th Brit. Weed Control Conf.* 163 (1974). Mode of action: G. F. Collet, *Weed Res.* **9,** 340 (1969). Long-term effect on soil: P. L. Huge, *Pflanzenschutz-Nachr.* **34,** 97 (1981). Brief review: P. Lours, *Def. Veg.* **24,** 91 (1970).



White crystals from benzene, mp 119-120.5°. Soly in water at 20°: 59 ppm. Sol in organic solvents. Vapor pressure at 20°: $<10^{-6}$ mm Hg. LD_{50} in mice (mg/kg): >1000 orally; in male, female rats (mg/kg): >2500, >2500 orally; 540, 315 i.p. (Kimmerle, Löser).

USE: Selective herbicide.

5965. Methacholine Chloride. [62-51-1] 2-(Acetyloxy)-*N,N,N*-trimethyl-1-propanaminium chloride; acetyl-β-methylcholine chloride; *O*-acetyl-β-methylcholine chloride; (2-hydroxypropyl)trimethylammonium chloride acetate; (2-acetoxypropyl)trimethylammonium chloride; trimethyl-β-acetoxypropylammonium chloride; Amechol; Provocholine. $C_8H_{18}ClNO_2$; mol wt 195.69. C 49.10%, H 9.27%, Cl 18.12%, N 7.16%, O 16.35%. Parasympathomimetic bronchoconstrictor. Prepn: R. T. Major, J. K. Cline, US **2040146** (1936 to Merck & Co.). Mechanism of ganglionic blockade in cats: R. L. Volle, *J. Pharmacol. Exp. Ther.* **158,** 66 (1967). Clinical diagnostic efficacy in bronchial asthma: S. L. Spector, R. S. Farr, *J. Allergy Clin. Immunol.* **56,** 308 (1975); J. G. Easton, I. Hirata, *Ann. Allergy* **50,** 171 (1983).



White, hygroscopic needles from ether, mp 172-173°. Slight odor of dead fish. Freely sol in water, alcohol, chloroform. Insol in ether. Aq solns are neutral to litmus. Should not be handled in very moist atmosphere. Bromide is less hygroscopic.

Antidote: Atropine.

THERAP CAT: Cholinergic. Diagnostic aid (bronchial asthma).

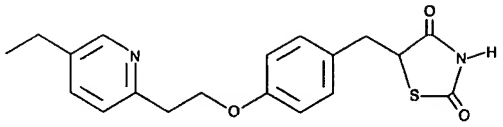
5966. Methacrifos. [62610-77-9] (2*E*)-3-[(Dimethoxyphosphinothioyl)oxy]-2-methyl-2-propenoic acid methyl ester; 3-hydroxy-2-methylacrylic acid methyl ester, *O*-ester with *O,O*-dimethyl phosphothioate; methyl (*E*)-3-(dimethoxyphosphinothioyloxy)-2-methylacrylate; CGA-20168; Damfin. $C_7H_{13}O_5PS$; mol wt 240.22. C 35.00%, H 5.45%, O 33.30%, P 12.89%, S 13.35%. Organophosphorus insecticide effective against arthropod pests in stored grains. Prepn: E. Beriger, L. Pinter, ZA **67 04184**; *eidem,* US **3594454** (1967, 1971 both to Ciba); *eidem,* BE **766000**; *eidem,* US **3923932** (1971, 1975 both to Ciba-Geigy). GLC determn of residues in stored grain: J. Desmarchelier *et al., Pestic. Sci.* **8,** 473 (1977). Efficacy and long-term stability: R. L. Kirkpatrick *et al., J. Econ. Entomol.* **75,** 277 (1982). Comparative field trial in stored sorghum: M. Bongston *et al., Pestic. Sci.* **14,** 385 (1983). Comprehensive description: R. Wyniger *et al., Proc. Brit. Crop Prot. Conf. - Pests Dis.* **1977,** 1033.

Product Information

Pioglitazone

Catalog No. 71745

CAS Registry No.: 111025-46-8
Formal Name: 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl] methyl-2,4-thiazolidinedione
MF: $C_{19}H_{20}N_2O_3S$
FW: 356.4
Purity: ≥98%
Stability: ≥1 year at -20°C
Supplied as: A crystalline solid
UV/Vis.: λ_{max}: 267 nm



Laboratory Procedures

For long term storage, we suggest that pioglitazone be stored as supplied at -20°C. It will be stable for at least one year.

Pioglitazone is supplied as a crystalline solid. A stock solution may be made by dissolving the pioglitazone in an organic solvent purged with an inert gas. Pioglitazone is soluble in organic solvents such as DMSO and dimethyl formamide. The solubility of pioglitazone in these solvents is at least 2.5 mg/ml.

Pioglitazone is sparingly soluble in aqueous buffers. For maximum solubility in aqueous buffers, pioglitazone should first be dissolved in DMSO and then diluted with the aqueous buffer of choice. Pioglitazone has a solubility of 100 µg/ml in a 1:1 solution of DMSO:PBS (pH 7.2) using this method. We do not recommend storing the aqueous solution for more than one day.

Thiazolidinediones (TZDs) are a group of structurally related PPARγ agonists with anti-diabetic actions *in vivo*.[1,2] Rosiglitazone (BRL49653) is a prototypical TZD and has served as a reference compound for this class of PPARγ ligands.[3]

Pioglitazone is a closely related TZD which also selectively activates the human PPARγ-1. Pioglitazone is about one tenth as potent as rosiglitazone, with an EC_{50} of about 500-600 nM for both human and mouse PPARγ.[4,5] In a transactivation assay using COS-1 cells transfected with full length human PPARα and RXRα, pioglitazone and rosiglitazone exhibit low level activation of PPARα at 1 µM and 5.4- and 4.2-fold activation, respectively, at a concentration of 10 µM.[4]

References

1. Willson, T.M., Cobb, J.E., Cowan, D.J., *et al.* The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones. *J. Med. Chem.* **39**, 665-668 (1996).
2. Cantello, B.C.C., Cawthorne, M.A., Cottam, G.P., *et al.* [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **37**, 3977-3985 (1994).
3. Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., *et al.* An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-acivated receptor γ (PPARγ). *J. Biol. Chem.* **270**, 12953-12956 (1995).
4. Sakamoto, J., Kimura, H., Moriyama, S., *et al.* Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem. Biophys. Res. Commun.* **278**, 704-711 (2000).
5. Willson, T.M., Brown, P.J., Sternbach, D.D., *et al.* The PPARs: from orphan receptors to drug discovery. *J. Med. Chem.* **43(4)**, 528-550 (2000).

Related Products

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